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Division of Dockets Management (HFA –305)
Food and Drug Administration
5630 Fishers Lane - Room 1061
Rockville, MD 20852

RE: *Current Good Manufacturing Practice for Combination Products; Guidance for Industry and FDA [Docket 2004D-0431]*

Dear Sir or Madam:

Abbott Laboratories submits the following comments regarding FDA draft guidance document "Current Good Manufacturing Practice for Combination Products," published in the Federal Register on October 4, 2004 at 69 FR 59239.

Thank you for the opportunity to provide these comments. We support the concept described in the guidance that each constituent part remains subject only to its governing current good manufacturing practice regulations when marketed separately and when manufactured separately as constituent parts of a combination that will later be combined.

Single-Entity Combination Products

For single-entity combination products, we recommend FDA further clarify its expectations regarding the application of current good manufacturing practice regulations during and after joining the constituent parts together. Lines 171-174 state, "FDA believes that compliance with both sets of regulations during and after joining these types of combination products can generally be achieved by using either the cGMP or QS regulations, e.g., by using the current good manufacturing practice system already operating at a manufacturing facility." Table 1 of the document identifies key current good manufacturing practice provisions to consider during and after joining together single-entity combination products. Based on this guidance it is reasonable for one to conclude that compliance may be achieved by using one set of regulations, cGMP or QS regulations, and addressing relevant specific requirements of the other set of regulations. Furthermore, risk assessments, a critical component of the quality system approach, enable manufacturers to identify which specific requirements of the other set of regulations are relevant to the combination during and after joining.

As the document continues, lines 207-208 state sponsors are to demonstrate "how they intend to achieve compliance with each set of regulations during and after joining the products together." Lines 235-236 state, "[o]nce the product is combined into a single

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entity...both sets of regulations apply..." Thus, it appears, that during an inspection, one may be required to demonstrate how compliance with the requirements of each set of regulations has been achieved. Such an approach seems contrary to FDA's intent. However, without more explicit language, it is easy to envision that the latter approach is what will be expected and that documented risk assessments used to define relevant elements of the other set of regulations may be viewed insufficient in demonstrating compliance with both sets of regulations.

We recommend the guidance document address the use of quality system risk assessments as a mechanism for determining relevant requirements of the other set of regulations and further clarify FDA's expectations relevant to its statements that "both sets of regulations apply."

Co-Packaged Combination Products

As with single-entity combination products, the guidance document proposes the application of both current good manufacturing practice regulations to co-packaged combination products. We recommend further differentiating co-packaged product products from single-entity products, especially when the packaging process does not adversely affect the combination. When considering the key cGMP provisions contained in Table 1 of the guidance document the necessity of applying such provisions to co-packaged products is not readily apparent.

For example, is it necessary to consider how these key cGMP provisions apply to device kits or trays[1] (also known as convenience kits) that contain a drug after the drug is added to the kit? If the drug is essentially a finished drug, what are the expectations regarding the application of the unique Quality System regulations, such as design controls, to the finished drug once joined with the device component of the combination product? Conversely, what are the expectations regarding the application of the unique drug cGMP regulations, such as calculation of yield or stability testing, to the device component of the co-packaged combination?

Because the language of the guidance document emphasizes the need to achieve compliance with each set of regulations during and after joining the products together it is unclear how one would address aspects of the regulations that do not appear to readily apply to co-packaged products. We recommend FDA provide additional guidance in this area. For example, describing circumstances where one set of regulations remains applicable to co-packaged products, such as when the packaging process does not adversely affect the single-entity products, and the use of risk assessments to determine whether relevant elements of the other set of regulations apply to the co-packaged product.

[1] We note Section VII, B.2 of the "Intercenter Agreement Between The Center for Drug Evaluation and Research and The Center for Devices and Radiological Health" provides that for convenience kits with a drug component, in which CDRH is the lead Center, the device cGMPs apply. FDA clarification that issuance of the Current Good Manufacturing Practice for Combination Products guidance document is not intended to superseded GMP assignments detailed in the Intercenter Agreements is recommended.

Communication of Combination Product cGMP Compliance Plans/Information

We recommend including in the guidance document provisions for ensuring field investigators are aware of the combination product cGMP compliance plans agreed to by the Center and sponsor. To avoid potential misunderstandings within the agency we recommend FDA staff commit to sharing combination product cGMP compliance plans with the appropriate District Office. Specifically, we recommend modifying the last sentence of section IV. A., by replacing "should" with "will," so it reads "FDA staff will communicate this information to the appropriate District Office."

Define "During and After Joining"

Define "during and after joining." This phrase is used extensively in the guidance document, and is critical to determining when two sets of cGMPs apply. It appears to mean during the joining together of the constituent parts and activities following their joining together. We recommend including a definition and supplementing with examples.

Guidance Document Reflect Quality Systems

To reflect FDA's move towards Quality Systems, we recommend changing the title of the document to "Application of Quality Systems to Combination Products," and subsequently emphasizing, within the body of the document, quality system approaches to meeting cGMP. Changing the title more accurately reflects the systems approach that FDA has adopted for devices[2] and is in the process of adopting for drugs[3].

Combination Products Subject to 510(k) Submission

FDA, in section IV, A of the guidance document, recommends manufacturers use pre-IND/IDE meetings to discuss with the agency cGMP issues applicable to combination products. Products subject to 510(k) submission, including combination products, generally do not fall within Center guidance for requesting pre-IND/IDE meetings. We recommend this guidance include a contact unit in CDRH where cGMP issues applicable to combination products may be discussed for combination products that are marketed via the 510(k) process.

Should you have any questions, please contact me at (847) 937-8197 or by facsimile at (847) 938-3106.

Sincerely,

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[2]In the final FDA quality regulations for devices (61 FR 52602), FDA changed the title of the regulation (part 820) from Current Good Manufacturing Practice (CGMP) to Quality System.

[3]In the draft guidance issued September 2004 by FDA on Pharmaceutical cGMPs, the introduction indicates that the guidance will help manufacturers implement modern quality systems and risk management approaches to meeting CGMP regulations. It further states, "[t]he guidance describes a comprehensive quality systems (QS) model...."